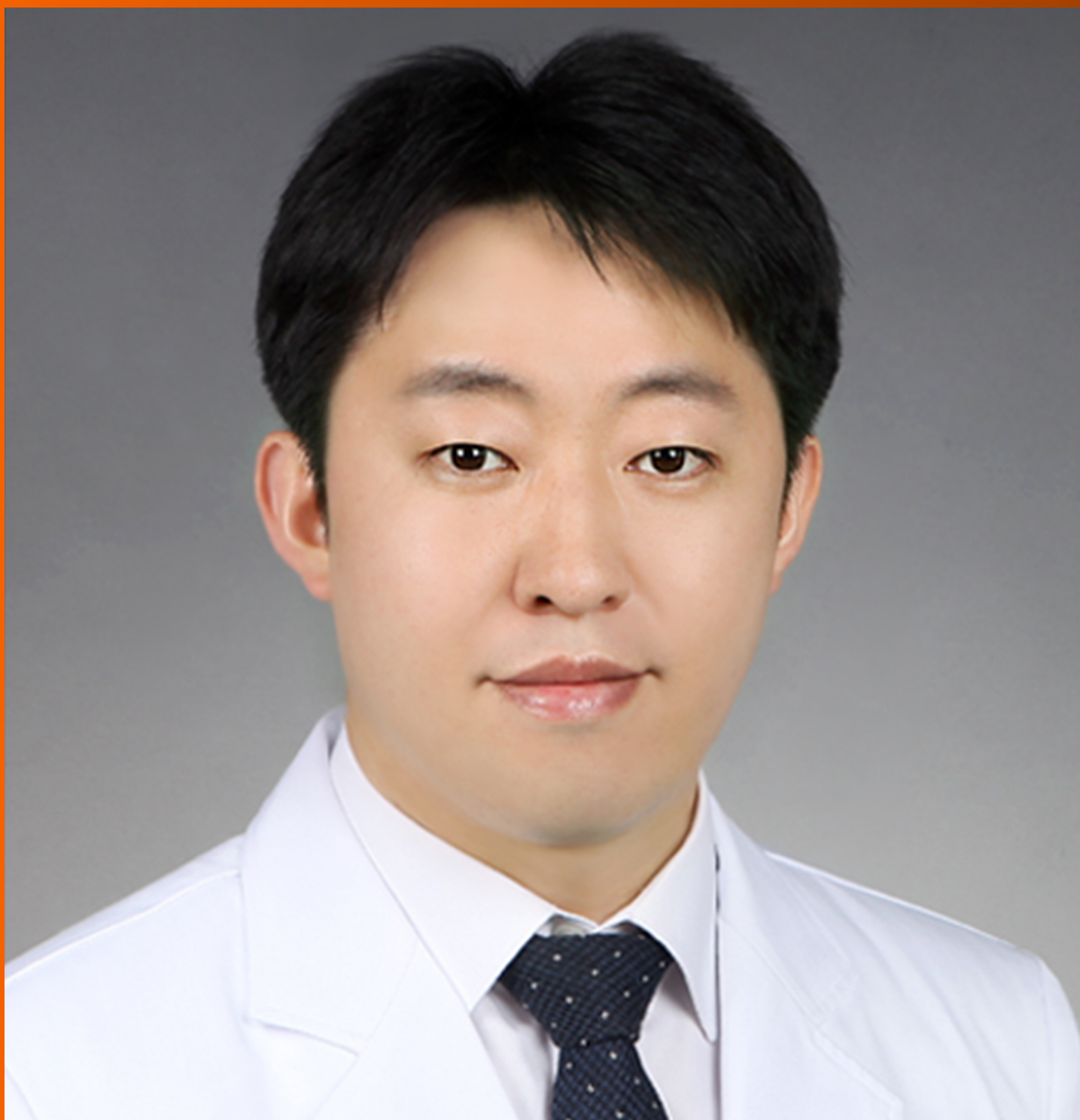


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WJGP mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal pathophysiology and covering a wide range of topics including disorders of the esophagus, stomach and duodenum, small intestines, pancreas, biliary system, and liver.

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Retrospective Cohort Study

Platelet count as a screening tool for compensated cirrhosis in chronic viral hepatitis

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Abstract

BACKGROUND

Simple tools for clinicians to identify cirrhosis in patients with chronic viral hepatitis are medically necessary for treatment initiation, hepatocellular cancer screening and additional medical management.

AIM

To determine whether platelets or other laboratory markers can be used as a simple method to identify the development of cirrhosis.

METHODS

Clinical, biochemical and histologic laboratory data from treatment naive chronic viral hepatitis B (HBV), C (HCV), and D (HDV) patients at the NIH Clinical Center from 1985-2019 were collected and subjects were randomly divided into training and validation cohorts. Laboratory markers were tested for their ability to identify cirrhosis (Ishak ≥ 5) using receiver operating characteristic curves and an optimal cut-off was calculated within the training cohort. The final cut-off was tested within the validation cohort.

RESULTS

Overall, 1027 subjects (HCV = 701, HBV = 240 and HDV = 86), 66% male, with mean (standard deviation) age of 45 (11) years were evaluated. Within the training cohort ($n = 715$), platelets performed the best at identifying cirrhosis compared to other laboratory markers [Area Under the Receiver Operating Characteristics curve (AUROC) = 0.86 (0.82-0.90)] and sensitivity 77%, specificity 83%, positive predictive value 44%, and negative predictive value 95%. All other

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tested markers had AUROCs ≤ 0.77 . The optimal platelet cut-off for detecting cirrhosis in the training cohort was $143 \times 10^9/L$ and it performed equally well in the validation cohort ($n = 312$) [AUROC = 0.85 (0.76-0.94)].

CONCLUSION

The use of platelet counts should be considered to identify cirrhosis and ensure optimal care and management of patients with chronic viral hepatitis.

Key Words: Chronic hepatitis B; Chronic hepatitis C; Chronic hepatitis D; Platelets; Cirrhosis; Non-invasive assessment

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Core Tip: Platelet count is a well-recognized surrogate marker for progression of liver disease, however a specific cut-off for cirrhosis has not been established. In this study, platelet counts can accurately stratify chronic viral hepatitis patients with cirrhosis; and a platelet count $> 143 \times 10^9/L$ appears to have the most clinical utility in ruling out cirrhosis across all chronic viral hepatitis. This widely available laboratory value may be useful in decision making for the management of patients with chronic viral hepatitis and represents a finding which may be of particular value in a primary care setting.

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INTRODUCTION

Globally, chronic hepatitis B, C, and D virus (HBV, HCV and HDV respectively) affect about 325 million people[1]. Progression of these viral infections is associated with serious complications including cirrhosis, hepatic decompensation, hepatocellular carcinoma, and death. With effective treatments for hepatitis B and C, the Centers for Disease Control and Prevention have advocated for widespread screening for viral hepatitis in adults[2,3]. There has also been a paradigm shift where primary care physicians are increasingly tasked with managing and treating these patients[4], and various programs have allowed for expanded care in areas with poor access to viral hepatitis care[5]. In addition, numerous efforts worldwide have aimed to increase the number of providers with the ability to manage chronic viral hepatitis, including the national viral hepatitis action plan 2017-2020 by the U.S. Department of Health and Human Services[6] and the Mukh-Mantri Punjab Hepatitis C Relief Fund program in India[7].

The decision of when and whom to treat in chronic viral hepatitis infections is often dependent upon the stage of liver disease[8,9]. Currently, liver biopsy is the gold standard for staging disease severity in patients with liver disease. However, liver biopsies are invasive, performed by a specialist and access may be limited in resource-poor regions. To date, no single routinely measured laboratory marker has been explored for the identification of cirrhosis. Although expert consensus suggests that thrombocytopenia, with a laboratory cutoff value of $< 150 \times 10^9/L$, is a surrogate marker for cirrhosis, this has mostly been demonstrated in patients with chronic HCV[10,11]. More recently, platelet counts have been used in conjunction with other markers. Current hepatology guidelines state that clinically significant portal hypertension can be identified by "liver stiffness > 20 - 25 kPa, alone or combined with platelet count and spleen size"[12]. Unfortunately, ultrasound-based techniques [such as Vibration Controlled Transient Elastography (VCTE)] providing an assessment of liver stiffness and cirrhosis are not widely available in all regions and to all healthcare providers.

Common serum laboratory tests, including platelet counts, have been included in



non-invasive markers of liver fibrosis or cirrhosis and have demonstrated clinical utility in the management of hepatitis C[9,13]. However, these non-invasive markers have not been shown to be as useful in chronic HBV due to its complex natural history[14,15]. Nonetheless, these tools have provided a cost-effective method to identify disease progression in patients with chronic viral hepatitis. Unfortunately, these tests require an on-line calculator as well as interpretation of various cutoff values and although often used by hepatologists and gastroenterologists, they remain unknown to primary care providers. Additionally, while their use for diagnosis of advanced fibrosis is widespread, they are not as powerful in determining cirrhosis as ultrasound-based methods[16,17].

With the increasing role of primary care providers in the management of chronic viral hepatitis, the development of a widely available and versatile tool in identifying patients with cirrhosis is clinically necessary. In this group of patients, additional management and treatment considerations may be required, as well as a referral to a specialist. In this study, we explore whether platelets or other commonly measured laboratory markers, alone, can be used as a simple and effective way to characterize the progression of viral hepatitis and whether a threshold can be identified for the development of cirrhosis.

MATERIALS AND METHODS

Study population

This retrospective, cross-sectional study consisted of patients infected with HBV, HCV or HDV and who underwent liver biopsy at the National Institutes of Health Clinical Center between 1985 and June 2019. Chronic viral hepatitis infection was established if patients demonstrated viral positivity for at least six months and/or histology consistent with the respective chronic infection. Chronic hepatitis B infection was established with the presence of hepatitis B surface antigen (HBsAg) in serum and positive HBsAg or hepatitis B core antigen staining on histology. Chronic hepatitis D co-infection was established with the presence of anti-HDV antibodies and HDV RNA in serum or positive hepatitis D antigen staining on histology in patients with chronic HBV. In patients who underwent biopsy after 1991, chronic hepatitis C was established using the presence of HCV RNA in serum for six months. In those who underwent biopsy prior to 1991, patients with presence of clinical and histologic features of non-A non-B hepatitis were later confirmed to have HCV infection by testing for HCV RNA using stored serum.

Patients with concomitant chronic non-viral liver diseases, multiple viral hepatitis (besides HBV/HDV co-infection), or HIV co-infection were excluded. In addition, patients were judged to be in adequate overall health to undergo liver biopsy and had no severe systemic diseases. All patients were enrolled in clinical research protocols approved by the National Institute of Diabetes and Digestive and Kidney Diseases Institutional Review Board and gave written, informed consent for participation. Pre-treatment liver biopsies were reviewed, and concurrent laboratory values were also collected using the NIH Biomedical Translational Research Information System. Laboratory results within two months prior to the liver biopsy and initiation of any treatment were utilized for analysis.

Liver histopathology

All liver biopsies were scored and analyzed by a single hepatopathologist (DEK). Ishak fibrosis scores were used to score hepatic fibrosis, ranging from 0 (no fibrosis) to 6 (cirrhosis)[18]. Cirrhosis was defined as a score ≥ 5 . Inflammation was scored using the modified histologic activity index (HAI), ranging from 0-18[19]. The total HAI score comprised of the summation of periportal inflammation, lobular inflammation, and portal inflammation.

Statistical methods

Training and validation cohorts: The entire cohort was randomly divided into training and validation cohorts using simple random sampling and a sample rate of 0.3. Selection was stratified by gender and virus type. Univariate comparisons of the two cohorts were conducted using student *t*-tests and chi-square tests where appropriate. Based on this analysis the training and validation cohorts were similar.

Biomarker selection: The training cohort was used to single out the best performing biomarker to identify cirrhosis status. Spearman's correlations were calculated in the

training cohort to determine the association between fibrosis and selected laboratory markers. Of the significantly correlated laboratory parameters, those with an absolute value of Spearman's R greater than 0.3 (moderate correlation) were selected for further analysis within the training cohort[20]. Logistic regression was used to create receiver operating curves and calculate the area under the curve (AUROC) of each selected laboratory parameter within the training cohort. Laboratory markers were log transformed to assure normality of the data. Sensitivity, specificity, positive predictive value, and negative predictive value were also used to measure performance. Delong Test was used to compare ROC curves for different laboratory parameters within the same sample group. Youden's index, as well as sensitivity, specificity, positive predictive value, and negative predictive value were all used to determine the optimal platelet cut-off point to predict cirrhosis. Once this analysis was completed in the training cohort, the most significant factor in the training cohort was tested in the validation cohort and by virus within the validation cohort through AUROC values, sensitivity, specificity, positive predictive value, and negative predictive value. Fibrosis-4 index (Fib-4) and AST (aspartate aminotransferase) to Platelet Ratio Index (APRI) were calculated using the established formulas[9,13]. All analysis was conducted using SAS 9.4 (Cary, NC, United States).

RESULTS

Study demographics

A total of 1027 untreated subjects with viral hepatitis were evaluated (HCV = 701, HBV = 240, HDV = 86). The mean age of the cohort was 45 years (SD: 11) and 66% of subjects were male. Baseline demographics for the training and validation cohorts are displayed in Table 1. In the training cohort, the mean Ishak fibrosis score was 2.4 (SD: 1.8) and 15% of patients were cirrhotic.

Mean platelet count in the training cohort was $187 \times 10^9/L$ (SD: 64). Mean alanine aminotransferase (ALT) and AST values were elevated within the training cohort [104 IU/mL (SD: 88); 70 IU/mL (SD: 55) respectively]. Mean albumin, prothrombin time, total bilirubin, and alkaline phosphatase values were within normal limits.

Using a single laboratory marker to identify cirrhosis

Laboratory markers commonly used to characterize liver disease were tested for their ability to identify cirrhosis within the training cohort (Table 2). These markers included transaminases, platelet count, total bilirubin, prothrombin time, albumin, and alkaline phosphatase. On Spearman's correlation of the training cohort, all tested laboratory markers appeared to be significantly correlated with Ishak fibrosis stage; however, only platelets, ALT, AST, alkaline phosphatase, and prothrombin time had Spearman correlations > 0.3 (Table 2).

Out of all of these laboratory markers, platelets performed the best at identifying cirrhosis compared to other laboratory markers (AUROC = 0.86, 95%CI 0.82-0.90), with all other markers with AUROCs ≤ 0.77 (Table 3). Prothrombin time had the next highest AUROC in the entire cohort (0.76, 95%CI 0.71-0.82). When comparing the ROC curves by the Delong test, platelets performed significantly better than all other tested laboratory markers in the training cohort ($P < 0.002$). Platelet counts compared favorably to both APRI [AUROC 0.84 (95%CI 0.80-0.88)] and Fib-4 [AUROC 0.88 (95%CI 0.85-0.91)].

Calculating a platelet cut-off for cirrhosis

The optimized platelet cut-off for detecting cirrhosis in the training cohort was $143 \times 10^9/L$ (sensitivity: 77%, specificity: 83%, positive predictive value: 44%, negative predictive value: 95%). Figure 1 shows an overall decrease in the distribution of platelet count by Ishak fibrosis in the training and validation cohorts. Additionally, the demarcated, calculated platelet cut-off of $143 \times 10^9/L$ appears to separate a majority of subjects with Ishak fibrosis ≥ 5 (Figure 1).

Platelet performance in validation cohort

The cutoff calculated in the training cohort was applied to the entire validation cohort and was also evaluated for each viral hepatitis. The performance of platelets to identify cirrhosis is demonstrated in Figure 2; platelets performed adequately in each virus (AUROC ≥ 0.81) and performed best in the HDV/HBV co-infection subset of the validation cohort (AUROC = 0.87). In the entire validation cohort, platelets performed

Table 1 Baseline demographics

	Training (n = 715)	Validation (n = 312)	P value
Age (yr)	45.6 (10.7)	44.5 (11.1)	0.1
Male/female (%)	66/34	66/34	1.0
Platelets ($\times 10^9/L$)	186.7 (64.4)	190.6 (68.2)	0.4
Alanine aminotransferase (IU/L)	103.8 (88.1)	105.1 (89.1)	0.8
Aspartate aminotransferase (IU/L)	69.9 (55.0)	68.0 (53.3)	0.6
Albumin (g/dL)	3.9 (0.46)	3.9 (0.39)	0.2
Alkaline phosphatase (IU/L)	82.3 (39.2)	79.0 (29.2)	0.1
Prothrombin time (s)	13.0 (1.3)	12.9 (1.1)	0.3
Total bilirubin (mg/dL)	0.81 (0.48)	0.77 (0.45)	0.2
Ishak fibrosis	2.4 (1.8)	2.3 (1.7)	0.3
HAI inflammation	8.0 (3.0)	7.9 (3.1)	0.5
HBV/HCV/HDV (%)	23/68/8	23/68/9	1.0

Values presented as mean (SD) unless otherwise noted.

Table 2 Spearman correlations between Ishak fibrosis and liver tests within training cohort

	R	P value
Platelets	-0.49	< 0.0001
AST	0.51	< 0.0001
ALT	0.37	< 0.0001
Alkaline phosphatase	0.35	< 0.0001
Prothrombin time	0.33	< 0.0001
Albumin	-0.30	< 0.0001
Total bilirubin	0.18	< 0.0001

Table 2 shows the calculated Spearman *R* and *P* value for the correlations between Ishak fibrosis and the indicated laboratory value. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

Table 3 Area under the curve using selected liver tests within the training cohort

Platelets	ALT	AST	Alkaline phosphatase	Prothrombin time
0.86 (0.82, 0.90)	0.65 (0.59, 0.71)	0.76 (0.71, 0.81)	0.76 (0.71, 0.81)	0.77 (0.71, 0.82)

Values presented as Area Under the Receiver Operating Characteristics curve (AUROC) (95% Wald confidence interval). Table 3 displays the calculated AUROC and 95% Wald confidence interval for each selected laboratory marker in identifying cirrhosis (Ishak ≥ 5) in the training cohort and the entire cohort. Overall, when compared by Delong test, platelets have a significantly greater AUROC value than each of the other laboratory values ($P > 0.002$). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

with an AUROC of 0.85 (95%CI 0.76-0.94) and performed as well as APRI [AUROC 0.82 (95%CI 0.74-0.90)] and Fib-4 [AUROC 0.86 (95%CI 0.80-0.93)]. In general, the optimal platelet cut-off had a higher negative predictive value than positive predictive values (Table 4).

For simplicity, it may be suggested that a platelet cut-off of $143 \times 10^9/L$ be rounded to $140 \times 10^9/L$ instead. The sensitivity, specificity, positive predictive value, and negative predictive values were not greatly altered in the validation cohort (73%, 86%, 48%, 95% respectively) (Table 5).

Table 4 Performance of optimal platelet cut-offs in validation cohort

	Platelet cut-off ($\times 10^9/L$)	AUROC	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Entire validation cohort	143	0.85 (0.76-0.93)	79	84	33	98
HBV	143	0.81 (0.53-1.00)	83	82	29	98
HCV	143	0.83 (0.72-0.94)	75	86	31	98
HDV	143	0.87 (0.74-1.00)	100	60	47	100

Table 4 displays the calculated cut-offs and sensitivity, specificity, positive predictive values, and negative predictive values for each the calculated optimal cut-off within the validation cohort. AUROC: Area Under the Receiver Operating Characteristics curve. HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Hepatitis D virus.

Table 5 Performance of platelet cut-offs in training cohort

Platelet counts ($\times 10^9/L$)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
130	67	91	57	94
140	73	86	48	95
143	74	83	44	94
150	78	78	38	95

Table 5 displays the calculated sensitivity, specificity, positive predictive values, and negative predictive values for four cut-off platelet counts within the training cohort.

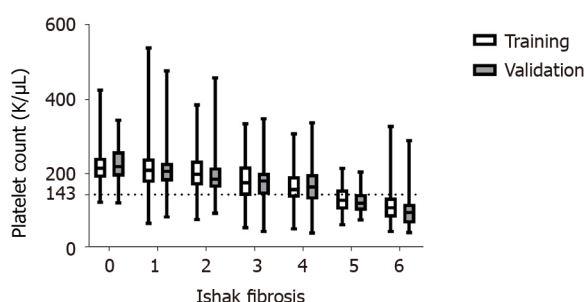


Figure 1 Platelet count distribution by Ishak fibrosis. This figure displays the distribution of platelets in the training and validation cohorts by Ishak fibrosis. The dotted line indicates the calculated optimal platelet cut-off ($143 \times 10^9/L$).

DISCUSSION

In the largest reported cross-sectional retrospective study of patients with chronic viral hepatitis evaluating routinely measured laboratory tests, platelet counts were identified as a surrogate marker for the development of cirrhosis. In comparison to other commonly performed clinical tests in a primary care setting, platelet counts performed the best and had the highest AUROC in identifying patients with cirrhosis. An optimized platelet cut-off value of $143 \times 10^9/L$ across all chronic viral hepatitis infections suggesting cirrhosis was validated. A rounded platelet count of $140 \times 10^9/L$ appears to show similar performance in identifying cirrhosis as well. Given that primary care providers are uniquely positioned in managing patients with chronic viral hepatitis, these results offer a simple and effective method to determine severity of liver disease in a primary care setting without additional testing. The ability to rule out cirrhosis through a simple surrogate marker may provide a simplified approach to connecting patients to treatment and optimal medical management.

Thrombocytopenia is often recognized as a complication of liver disease and has been used as a surrogate marker for varices, portal hypertension, and increased risk of hepatocellular carcinoma; typical complications of cirrhosis[21-23]. Mechanistically,

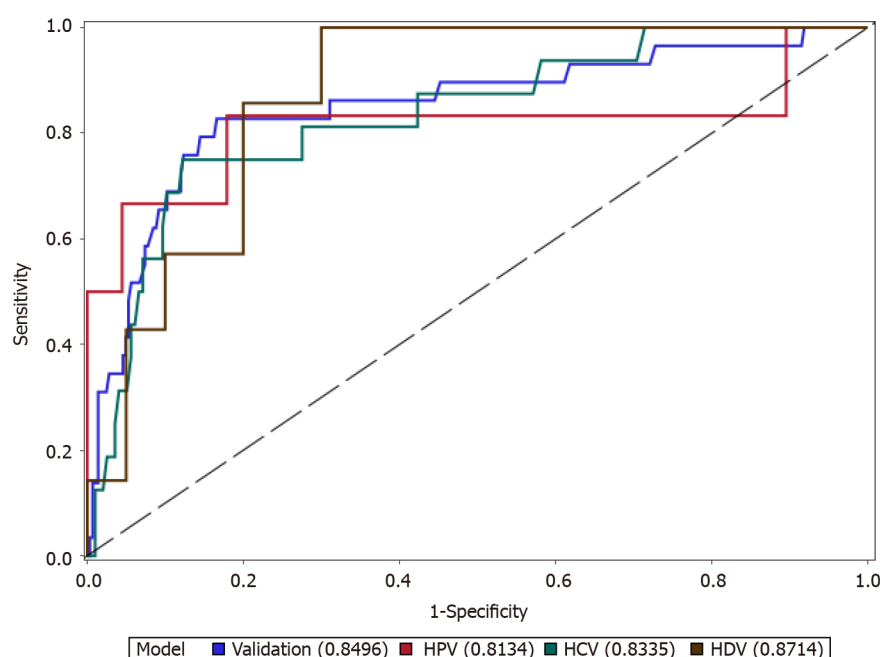


Figure 2 Receiver operating characteristic curves for platelet performance. Receiver operating characteristic curves testing the performance of platelets in identifying cirrhosis in chronic viral hepatitis patients. Area Under the Receiver Operating Characteristics curves (AUROC) were calculated for the entire validation cohort and by virus subgroups within the validation cohort. AUROC values are displayed in the figure key. HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Hepatitis D virus.

there are several possible explanations for the thrombocytopenia in chronic liver disease; such as, splenic sequestration of platelets, decreased platelet production, and decreased thrombopoietin activity[22,24]. Historically, only thrombocytopenia below $50 \times 10^9/L$ has demonstrated clinical relevance[25]. Recently, various scores incorporating platelet counts have been proposed as a surrogate screening tool for complications of portal hypertension, most notably high-risk varices, including the Baveno VI criteria, the expanded Baveno VI criteria, and the albumin, bilirubin and platelet criteria (ABP criteria)[21,26,27]. In these scores, the suggested platelet count cut-offs range from $110 \times 10^9/L$ to $150 \times 10^9/L$. Nonetheless, these models are restricted to patients with an established diagnosis of cirrhosis.

Additionally, platelets have been incorporated into non-invasive biomarkers of fibrosis such as Fib-4 and APRI, formulas typically utilized by sub-specialists[9,13]. Non-invasive biomarkers have been gaining interest as a useful tool in risk stratification in liver disease. However, transaminases, including AST are required for their calculation. This represents a significant drawback in the primary care setting due to increased evidence in certain regions of the world advocating for limiting hepatic screening panels to ALT and alkaline phosphatase[14,28]. Likewise, the cost-effectiveness of this strategy has also been described[29]. Over time, this approach has become an integral part of guidelines, including from the British Society of Gastroenterology[30]. Additionally, these indexes do not perform as well as patented biomarkers (FibroTest, FibroSure, Enhanced Liver Fibrosis) which are not widely available and are costly[31,32]. Therefore, in this context the use of a simple tool, such as platelet counts alone, can be a valuable tool for following patients with viral hepatitis prior to developing cirrhosis. In our cohort, platelet counts alone performed similarly to calculated non-invasive markers. This study demonstrates that thrombocytopenia below $143 \times 10^9/L$ on its own is of clinical importance in viral hepatitis and is a useful single laboratory test to rule out cirrhosis.

According to the World Health Organization, health equity has still not been achieved by countries of all socioeconomic levels. In order to breach this gap in care, an increasing number of primary care physicians are being trained to care for patients with chronic liver disease through programs and resources such as Project ECHO, HepCCaTT (offering care for HCV), and the HBV Primary Care Workgroup[5,33-35] (all in the United States) or the Mukh-Mantri Punjab Hepatitis C Relief Fund in India[7]. However, chronic liver disease is just one of many chronic illnesses that primary care physicians are called upon to manage in these settings. The utility of other non-invasive markers may be limited in resource poor-settings. Both Fib-4 and APRI require multiple laboratory marker measurements, calculations, and knowledge

of validated cut-offs for correct interpretation[9,13,32]. VCTE, while simple and useful technology, is expensive and may not be available at all centers of care. In addition, complex algorithms including a sequential use of non-invasive markers to improve their accuracy have also been suggested[36,37]. These non-invasive markers are useful in specialist care settings, but might not be optimal in resource limited settings where primary-care physicians are the main point of care.

While platelet count has been proven to be an important indicator of liver disease progression, it is important to note that the platelet counts represented in this retrospective single center study's cohort may differ from those seen in a typical primary care setting. Given the specialized setting of the National Institutes of Health, this population may have a higher prevalence of cirrhosis than the typical primary care setting, and this may enhance the performance of platelet count as a marker of cirrhosis within this study. This study proposes the use of a single, commonly measured laboratory marker to monitor the progression of chronic viral hepatitis and identifies a clinically relevant cut-off for clinical decision making and to rule-out cirrhosis. Further studies would provide more information about the clinical outcomes of these patients, on what the degree of thrombocytopenia may imply for these patients and how platelet counts should be included in non-invasive monitoring algorithms. The strength of this study lies in the large cohort of chronically infected patients with histology and three etiologies of viral hepatitis with the inclusion of patients with chronic delta hepatitis.

CONCLUSION

While platelet count has been established as a surrogate marker for disease progression, a specific cut-off for cirrhosis has not been established. Platelet counts can accurately stratify chronic viral hepatitis patients with cirrhosis, a finding which may be of particular value in a primary care setting. As a potential non-invasive biomarker, a platelet count $> 143 \times 10^9/L$ or the rounded value $140 \times 10^9/L$ appear to have the most clinical utility in ruling out cirrhosis across all chronic viral hepatitis. This routine and widely available laboratory value may be useful in the identification of patients with cirrhosis from chronic viral hepatitis which has downstream consequences related to their treatment and management and should be further explored for these purposes.

ARTICLE HIGHLIGHTS

Research background

The diagnosis of cirrhosis in patients with chronic viral hepatitis has both treatment and management implications. Identifying these patients is crucial in order to ensure proper care, prevent complications of cirrhosis and for judicious allocation of resources.

Research motivation

With an increasing reliance on primary care in management of chronic viral hepatitis, reliable simple non-invasive assessments of cirrhosis are needed in order to identify cirrhosis and to determine requirement of referral to specialized care.

Research objectives

To evaluate the performance of single laboratory markers, with an emphasis on platelet counts, to identify development of cirrhosis in patients with chronic hepatitis B virus, hepatitis C virus, and hepatitis D virus infection.

Research methods

Retrospective study comparing the accuracy of single laboratory markers in determining cirrhosis (defined as Ishak fibrosis score ≥ 5). Area Under the Receiver Operating Characteristics curve (AUROC), sensitivity, specificity, positive predictive value and negative predictive value were measured first in a training cohort and then in a validation cohort.

Research results

In a cohort of 1027 subjects, compared to other single laboratory markers, platelet counts performed the best at identifying cirrhosis [AUROC 0.86 (0.82-0.90)] and sensitivity 77%, specificity 83%, positive predictive value 44%, and negative predictive value 95%. The optimal cut-off point was $143 \times 10^9/L$. This performed equally well in a validation cohort.

Research conclusions

Platelet counts are the most reliable single serological marker in ruling out cirrhosis in patients with chronic viral hepatitis. Thrombocytopenia can potentially be used in the primary care setting for management of patients with viral hepatitis.

Research perspectives

Future research directions include validation of this cut-off value of platelet counts in other cohorts of patients with liver disease and evaluation of longitudinal trends of thrombocytopenia.

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